Isoflurane-sparing Effect of Fentanyl in Swine

Relevance and Importance

In this issue of Anesthesiology, Moon et al. report that the isoflurane-sparing effect of fentanyl is much less in young swine than that reported in other species, including and especially humans. In these studies, they found that isoflurane minimum alveolar concentration decreased by an average of 24.5%, 29.9%, and 45.9% with constant intravenous infusion doses of fentanyl of 50, 100, and 200 μg · kg⁻¹ · h⁻¹, respectively. These fentanyl doses corresponded to average, steady-state plasma fentanyl concentrations of 14, 26, and 59 ng ml⁻¹, respectively. These doses are considerably larger than those used clinically in humans or other species.

As a veterinarian engaged in anesthesia research, teaching, and clinical activities with a wide range of animal species, including swine, at a university-based veterinary medical teaching hospital, I value and welcome this new information. I judge it important because it provides baseline information necessary to upgrade my clinical practice and enables me to better advise veterinary medical students and other health science colleagues on the actions of opioids in a species of importance to both clinical veterinary medicine and, more broadly, the biomedical research community.

However, why should a paper describing pharmacodynamics of opioids in swine be published in Anesthesiology, a journal of a clinical society devoted to human health care? Although information on fentanyl minimum alveolar concentration interaction in the dog and subsequently in human patients has been described in this Journal, one could argue that additional descriptive information in a nonhuman species is more appropriate for veterinary medical journals, such as the American Journal of Veterinary Research (a journal of the American Veterinary Medical Association), Veterinary Surgery (the official journal of both the American College of Veterinary Anesthetists and the American College of Veterinary Surgeons), or Laboratory Animal Science (a publication of the American Association for Laboratory Animal Science). Before attempting to justify the wisdom of the Editor in Chief of Anesthesiology in accepting the manuscripts in question, some background information is in order.

First, opioids have achieved prominence as principal drugs in the anesthetic management of human and selected veterinary (e.g., dogs) patients with poor cardiac reserve undergoing some types of major surgery, because of their widespread clinical use, opioids also often are selected for animal models of human health care problems (e.g., cardiac and transplant surgery). Opioids also are administered to animals to learn more about their general pharmacokinetic and pharmacodynamic actions and mechanisms.

Second, the existence of species differences in the pharmacologic actions of drugs important to the clinical practice of anesthesia is widely recognized. A notable example is the marked difference in anesthetic potency of nitrous oxide in humans and animals, including swine, an example that has some similarities in principle to the comparative value of the work of Moon et al. highlighted here.

Third, the use of swine in biomedical research, education, and testing has grown rapidly in the past decade. They share many physiologic and anatomic similarities with humans, and for other reasons, they have become valuable models for a variety of applications and study, including, for example, cardiovascular surgery, pancreatic and liver transplantation, wound healing, and shock. Unfortunately, there are little objective data of the nature that we have grown to expect on the action in swine of commonly used injectable anesthetic drugs. As a result, drug management schemes, especially for highly invasive operations associated with surgical models, often is derived and transposed directly from comparable surgery in humans. The prevailing attitude by most of us is that, if the technique is appropriate for humans, likely with little or no adjustment it will serve us satisfactorily for similar animal-related circumstances. This usually is justifiable, because a great deal of work with animals first is used to help define initial uses in humans. However, this reasoning is not infallible. Personal experiences with...
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swine in the laboratory and associated with common operations on client-owned swine under veterinary hospital conditions suggest that a direct carryover of opioid anesthetic protocols (including and especially drug dosage) from human patients to swine is inappropriate: the anesthetic that results is often inadequate for optimal operating conditions and humane treatment of the animal and, especially in laboratory situations, may contribute to misleading results and faulty experimental conclusions. The work of Moon et al. with fentanyl clearly strengthens this opinion.

To return to the question why publish a paper describing pharmacodynamics of fentanyl in swine, the following reasons are offered.

First, the results of Moon et al. are informative, broadly interesting, and derived from good work that meets the rigid, high standards of a journal that proffers to cover the spectrum of the science and clinical practice of anesthesia.

Second and perhaps more compelling is that ANESTHESIOLOGY has a responsibility to its readers to report work informing them about important species variability in response to drugs and anesthetic protocols. The Journal is read widely by anesthesiologists and members of the broader biomedical community interested in the newest information on anesthesia. This group includes not only physicians and other human health-care professionals but veterinarians and basic scientists, such as physiologists and pharmacologists. It is common to see in the Journal (and for that matter, in other major biomedical journals) articles and references to articles reporting work in which swine and opioid anesthetic techniques incorporating neuromuscular blockade were used. Thus, readers of ANESTHESIOLOGY regularly are faced with interpreting results of laboratory studies using swine as an animal model of circumstances closely depicting clinical conditions or in determining more basic information.

Third, some anesthesiologists regularly lead and/or participate in laboratory studies involving swine. Results of poorly designed studies that use inappropriate anesthetic techniques or animal models usually are incomplete and may be grossly misleading. Consider, for example, the extreme case involving a surgical procedure in which the anesthetic protocol in use does not produce anesthesia. Inhumane treatment of the animal is unacceptable and requires no further comment. The somatic and visceral responses of the animal to the pain accompanying surgery also add unnecessary confounding variables; it is simply "bad science." Beyond this, the loss of time by the investigators, their support staff, and the people involved in the manuscript review process to communicate well intended but misleading information is not a trivial matter.

Finally, some anesthesiologists and other frequent readers of ANESTHESIOLOGY, by virtue of their interests and clinical training or focused expertise, commonly are asked to serve on institutional animal care and use committees and/or are consulted regularly by members of such committees for expert opinion. Their actions heavily influence research involving animals. These individuals likely show a common characteristic: They consistently rely on ANESTHESIOLOGY as a primary focus for updates in the field.

Careful examination of species differences in response to drugs often leads to progress in the search for mechanisms of drug action and additional relevant information. Thus, the work of Moon et al. is of likely importance to readers with an interest in the broader scope of general pharmacokinetic and pharmacodynamic actions of opioids. Moon et al. showed that fentanyl infusion reduced the minimum alveolar concentration of isoflurane in swine but that much larger doses were required compared to other commonly studied species. These results complement those of recently reported studies of morphine actions in isoflurane-anesthetized monkeys, dogs, and adult miniature swine. In these studies, referenced by Moon et al., the reduction of isoflurane minimum alveolar concentration in swine after an intravenous bolus dose of morphine (2 mg/kg) was of less magnitude (e.g., 13% reduction at 35 min after injection in swine versus a 50% decrease at 35 min in dogs and 55% at 53 min in monkeys) and the isoflurane minimum alveolar concentration depression was of substantially shorter duration compared to the actions in the other two species. Therefore, it appears that swine represent a point further from humans on a graphic summary of the spectrum of species versus opioid action. Such species differences may be related to pharmacokinetic or pharmacodynamic factors or both. The relatively small and often inconsistent differences in pharmacokinetic profiles of opioids in the various species studied suggest that what the body does to the drug is not the generally prominent factor with regard to the actions of opioids considered here. Likely of greater importance in explaining species-related inhalation anesthetic-sparing effects is species-related differences in opioid receptor type, density, and distribution.

Use of this information to "get to the bottom line"

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depends on the interest and intent of the reader. For example, if Moon et al.'s data are to be used in a practical manner, such as for designing or interpreting anesthetic management schemes for a highly invasive surgical procedure in swine, the message is clear. Use of fentanyl as a sole or primary drug component of that scheme at doses similar to those used in human patients under similar circumstances is inadequate for proper surgical conditions and most likely results in inhumane conditions for the animal. If, on the other hand, the data are intended as a reflection of the magnitude of analgesia resulting from fentanyl, the interpretation is less clear. Confusion results because analgesia is presumably only one component of the animal's response that serves as an endpoint for determining minimum alveolar concentrations (i.e., move or no move).

Opioids, including fentanyl, are known to cause central nervous system stimulation and, for example, result in locomotor activity in some otherwise unmedicated animals, such as mice and horses. Effects such as this may confound interpretation of changes in minimum alveolar concentration because the endpoint of our observations is the sum of two opposing effects: an analgesic or central nervous system depression effect and an anecic or stimulatory effect. For example, we completed a study in which isoflurane-anesthetized horses were given morphine (2 mg/kg, intravenous) under conditions similar to those reported above for swine, dogs, and monkeys. In the absence of morphine, we found no more variability in the isoflurane minimum alveolar concentration than has been reported for horses. However, after morphine, the maximal change in isoflurane minimum alveolar concentration ranged from a 19% decrease in minimum alveolar concentration to a 56% increase in two of these six horses had a decrease in minimum alveolar concentration greater than 10% after morphine, and the other four had an increase of more than 10%). Does this mean that no analgesia was imparted by the relatively large dose of morphine used in our horses? Probably not. For example, studies of fentanyl in unanesthetized horses and mice have shown that both analgesia and increased locomotor activity results from fentanyl and morphine, respectively. Might such an effect occur in swine and therefore confuse some interpretations of Moon et al.'s data. Perhaps, because awake swine are known clinically to be stimulated by at least some opioids.

Regardless, the work of Moon et al. adds meaningfully to current knowledge of opioids in a practical and a theoretical way, and its appearance here is warranted. Like most good reports appearing in Anesthesiology, it leaves us with not only an answer but more issues to investigate and debate.

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References


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